Big LDL drops with PCSK9 inhibition in grouped phase-2 studies

ESC

Amsterdam, the Netherlands – An analysis of four phase-2 studies testing the effectiveness of **AMG145** (Amgen), a human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), showed the drug reduces LDL cholesterol by 43% to 64%, depending on the dose used.

The analysis combines data from studies testing AMG145 as part of different regimens, including as monotherapy and combining it with statin therapy, and different patient groups, including those with heterozygous familial hypercholesterolemia (FH) and statin-intolerant patients.

Presenting the results here at the European Society of Cardiology (ESC) 2013 Congress, **Dr Frederick Raal** (University of Witwatersrand, Johannesburg, South Africa) said that although lowering LDL cholesterol is the cornerstone of CVD prevention, "existing therapies to lower LDL cholesterol might not be well tolerated, and not all treated patients achieve LDL-cholesterol goals at tolerated goals."

PCSK9 plays a key role in the metabolism of LDL cholesterol, explained Raal. PCSK9 antibodies inhibit the PCSK9 protein, which binds to LDL receptors, resulting in their degradation so that fewer are available on liver cells that remove excess LDL cholesterol from the blood. By blocking the PCSK9 pathway, the new monoclonal antibodies upregulate the recycling of LDL receptors, thereby lowering LDL.

To date, phase-2 studies have shown that AMG145 "rapidly and robustly" lowers LDL cholesterol, as well as results in favorable improvements in other lipids. The ESC analysis combined data from these four trials, including 1252 patients, to assess efficacy of the drug across clinically important subgroups, including background lipid therapy, said Raal.

More than 1200 patients in phase-2 studies

In the **MENDEL** study, researchers tested AMG145 administered subcutaneously every two weeks or every four weeks in hyperlipidemic patients not treated with statins. LAPLACE-TIMI 57 tested the same dosing strategy but in patients treated with a statin. In the RUTHERFORD study, AMG145 was administered monthly in heterozygous FH patients treated with a statin; the GAUSS study tested the same dosing regimen in statin-intolerant patients. All studies were 12 weeks in duration.

In the studies, mean LDL cholesterol was 135 mg/dL at entry. The maximum 140-mg dose of AMG145, administered twice monthly, resulted in a 64% reduction in LDL cholesterol, as measured by ultracentrifugation. The 70-mg and 105-mg doses, administered twice monthly, reduced LDL cholesterol by 43% and 56%, respectively. Administered every four weeks, the highest 420-mg dose resulted in an LDL-cholesterol reduction of 57%; the lower 280-mg and 350-mg doses led to decreases of 45% and 50%, respectively.

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"Because of the marked reduction in LDL cholesterol, a large percentage of patients achieved LDL targets," said Raal during the ESC presentation. "If we look at the LDL target of 2.6 mmol/L, or 100 mg/dL, over 90% of patients achieved this target with the maximum twice-monthly dosing and nearly 90% achieved this target with the four-weekly dosing." When the more stringent target of LDL cholesterol <70 mg/dL was used, 80% of patients treated every two weeks and 60% of patients treated every two weeks met the goal.

Raal said AMG145 also reduced apolipoprotein B and lipoprotein(a) in a dose-dependent manner, and showed modest increases in apolipoprotein A1 and HDL cholesterol.

Speaking with **heart*wire***, **Dr Sanjay Kaul** (Cedars Sinai Medical Center, Los Angeles, CA), who was not affiliated with the analysis, said he is not a proponent of combining studies that include a clinically heterogeneous patient population. Despite this, the reduction in LDL cholesterol with the compound is impressive, said Kaul, although he is unsure what this will mean in terms of clinical events.

"If you're a believer of the lower-is-better hypothesis, which in my opinion remains not yet validated, then you're

going to be excited by the prospect of this drug," he said. "But I don't believe in the lower-is-better hypothesis because it hasn't been proven."

The current **American College of Cardiology**/**American Heart Association** guidelines for secondary prevention recommend lowering LDL cholesterol to <100 mg/dL (class I recommendation, level of evidence C). It is driven by epidemiological evidence, imaging studies, and animal data, said Kaul, and not randomized trials with outcome data to inform the recommendation. The evidence for treating LDL cholesterol to <70 mg/dL is even weaker, he added.

"So even if we lower LDL cholesterol to the 30s, 40s, and 50s with a very potent agent, is it going to translate into an incremental outcome benefit?" Kaul asked. "It's an open question. Before we jump on the bandwagon of these drugs, we have to acknowledge that the lower-is-better hypothesis remains a hypothesis at this point."

Good LDL reductions—what next?

Overall, Raal said the data support moving AMG145 into larger phase-3 efficacy studies. Although his presentation focused primarily on the effectiveness of the agent, a separate poster addressing safety suggests the drug is "remarkably safe" and, at this point in time, there does not appear to be any serious adverse events associated with its use.

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Dr Prediman Shah (Cedars Sinai Medical Center) also commented on the results for **heart*wire***. He said that although statins remain the gold standard for lowering LDL cholesterol, about 20% of individuals cannot tolerate the medications. In other cases, patients are unable to get their LDL cholesterol down low enough to get to goal. In addition, homozygous FH patients lack LDL receptors and don't respond to statins, and heterozygous FH patients only partially respond to the drugs. PCSK9 antagonists are only available subcutaneously—a drawback that might be a "tolerable nuisance" for patients with no other alternative.

"It is in these subgroups of at-risk population that a nonstatin drug would be desirable," said Shah. "I believe the data so far on PCSK9 inhibition as a statin alternative or statin add-on for LDL-cholesterol lowering are quite good from all the phase-2 trials of the Sanofi and Amgen compounds, raising the expectation that, if longer-term safety and event reduction can also be demonstrated, these agents could have an important role in the toolbox of cardiologists."

However, the long-term safety and efficacy of PCSK9 antagonists are not yet known, and although the lipid effects are impressive, CV event reduction remains to be proven, noted Shah. In order to keep the study size manageable, he suggests that a noninferiority trial with the injectable agents would be a reasonable option.

To **heart*wire***, Kaul agreed with Shah, noting that 12 weeks is too short to determine the safety of the agents. Although there is a track record of using monoclonal antibodies in oncology and rheumatology, there are very few effective therapies in those settings. In cardiology, there are other available agents, like statins, so the bar PCSK9 antagonists must clear will be higher. In addition, cost will be an issue. A month's supply of a generic statin costs approximately $10 per month; these new drugs could cost as much as $3000 per month, said Kaul.

The analysis presented at the ESC was financially supported by Amgen. Kaul and Shah report no conflicts of interest.

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